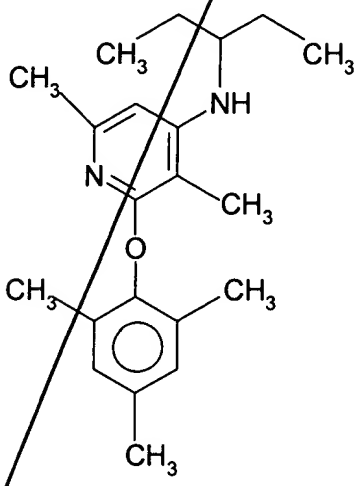
35. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug is



or a pharmaceutically acceptable salt thereof.

36. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug is an antipsychotic.

37. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug is ziprasidone.

38. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug is selected from griseofulvin, nifedipine, and phenytoin.

REMARKS

Applicant has amended the claims to obviate and/or overcome some of the points raised by the Examiner in the Office Action. Support for the amendments is discussed below, together with a discussion of how the amendments advance the prosecution of the application. Sheets entitled "VERSION MARKED UP TO SHOW CHANGES MADE" have been appended to this response to indicate the exact nature of the amendments.

The Section 112 Rejections

Per paragraph 2, claims 1, 7, 11, 15, 19, and 27 stand rejected for using "HPMCAS" which, according to Japanese unexamined patent application (Kokai) No. 57-176907, may be a trademark or a trade name. The Examiner took the alternative position that if HPMCAS is not a trade designation, the claims are indefinite because of the use of HPMCAS itself, i.e., the acronym.

The rejection is traversed in part because HPMCAS is not a registered trademark or other proprietary registered trade designation, at least not in the United States. Applicants have checked by looking for "HPMCAS" as a trademark in the trademark files of DIALOG® data base, and were unable to find any registration in any country. Applicants also searched using the exact name as in JP 57-176907 ("hydroxypropyl methyl cellulose acetate succinate") with the same result. It is thus believed that HPMCAS is not a registered trademark. Regarding the Examiner's alternative rejection on the basis that the claims are indefinite because Applicants have used an acronym, Applicants have placed the polymer's full name in claim 1 followed by "(HPMCAS)". It is accordingly respectfully submitted that Applicants have complied with the Examiner's suggestion and have thereby obviated the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Claims 6, 7, and 22, claim 15, and claim 33 were also rejected on similar grounds of having used the acronyms "MFD", "AUC", and "CRH", as also set forth in Paragraph 2.

In response, Applicants have amended claim 6 by replacing "MFD" with "model fasted duodenal (MFD) solution", as supported at page 5, line 3. To improve clarity, the word "solution" has also been added to claims 7 and 22 to complete the description of MFD solution.

Also, Applicants have replaced "AUC" in claim 15 with "area under a curve (AUC) plotting the serum or plasma concentration of drug along the ordinate against time on the abscissa", as defined at page 6, lines 28-30.

Also, Applicants have replaced the acronym "CRH" in claim 33 with "corticotropic releasing hormone (CRH)", as supported at page 9, lines 1-2.

All of the foregoing amendments are in compliance with the Examiner's suggestion regarding how the use of pure acronyms, without definition, should be avoided.

The Examiner further questioned Applicants' use of "in a use environment" and took the position that it is confusing. Applicants respectfully disagree and submit the term is readily understood in view of Applicants extensive explanation, definition, and description. The term denotes the environment or medium to which Applicants' claimed compositions can be added (i.e., for testing in an in vitro fluid) or administered (i.e., to the gastrointestinal tract, for therapy). The term thus accounts for the fact that a use environment can be in vitro or in vivo. The term, plus the types of in vitro and in vivo tests associated with a use environment, is all discussed and defined, for example, at page 5, lines 1-6 et seq. See also the text at page 17, line 26 to page 20, line 8.

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The Examiner, in paragraph 3, rejected claims 28-38 on the basis that the phrase "said compound", recited in each claim, has no antecedent basis. Applicants have amended each of claims 28-38 claim by changing "said compound" to "said drug" in accordance with the antecedent basis provided in prior claims. It is respectfully submitted that the rejection has been obviated, and it is requested that it be withdrawn.

The Examiner stated in paragraph 4 that claims 2, 8, 14, and 18 are confusing and are not examined on the merits. Applicants' are puzzled as to why these claims would be confusing, but assume any confusion likely arises out of the term "dose to aqueous solubility ratio". Applicants note that a dose to aqueous solubility ratio is simply a measure of a drug's relative aqueous solubility. A higher number indicates relatively poorer solubility while a lower number indicates relatively better solubility. The term is fully defined and discussed, inter alia, at page 7, lines 16-28.

Applicants have made some corrective amendments as well. In claims 2, 8, 14, and 18, the word "decribed", a misspelling of "described", has been changed to "defined" for continuity with the preambles of the remaining claims.

In view of Applicants' amendments and explanation as presented above, it is submitted that the formal rejections have been overcome. Withdrawal of all of the formal rejections is respectfully requested.

The art rejections

Claims 1, 4, 5, 7, 10, 11, 13, 15, and 17 stand rejected under 35 USC 102(b) as anticipated by JP (Kokai) No. 57-176907.

Claims 1, 4, 5, 7, 10, 11, 13, 15, 17, and 23-26 stand rejected under 35 USC 102(b) as anticipated by JP (Kokai) No. 2-15027.

Claims 1, 7, 11, 15, 36, and 38 stand rejected under 35 USC 102(b) as being anticipated by Nakamichi et al., US 5,456,923.

In each of the anticipation rejections the Examiner emphasized that if the prior art teaches a composition, the process of preparing it is not critical. The Examiner took the position that the process of making a composition does not distinguish the composition over the prior art. It is believed the Examiner was contending that the term "spray drying" does not distinguish the spray dried dispersions which constitute an element of Applicants' claims from dispersions made by processes other than spray drying.

The rejections are traversed on the basis that none of the references discloses a spray dried dispersion of HPMCAS and a sparingly soluble drug. It is

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Applicants' position that they are claiming a composition comprising a spray dried dispersion, and that such dispersions are different from other dispersions in terms of the drug solubility produced. That is, Applicants have determined that the method of making the dispersion affects the solubility of the dispersed drug. It is Applicants' position that, since spray drying produces a dispersion with demonstrably different properties in terms of drug solubilization, that spray dried dispersions are different from other dispersions, and therefore claimable as such. Thus, a process limitation can indeed affect the quality of the dispersion which comprises Applicants' claimed compositions, in contrast to the examiner's contention that process makes no difference to the composition.

First, it is noted that the instant application is a continuation of Application No. 09/131,019 (the "parent case") in which Applicants previously abundantly demonstrated the superiority of their compositions over Nakamichi, in particular in their response dated October 9, 2000, which included the Rule 132 Declaration of Dwayne T. Friesen. All of the arguments from that response, including the Declaration, are incorporated herein by reference, and a copy of that response, including the Declaration, is included herewith as Exhibits A and B for consideration by the Examiner. In brief, the point Applicants wish to make is that different qualities of dispersions, as measured by the differences in solubility of the drug incorporated therein, are produced according to the method used to make the dispersion. Applicants, *inter alia*, by means of the aforementioned Rule 132 Declaration, have already clearly demonstrated that their spray dried dispersions are generally unexpectedly much better than the rotary evaporated dispersions disclosed in Nakamichi for comparison purposes and, by extension, better than Nakamichi's dispersions produced by a twin screw extruder. The Examiner is urged to review Exhibits A and B since, for the sake of brevity, Applicants prefer not to repeat them in the instant response.

In brief, Applicants submit that they have previously shown that they are non-obvious over Nakamichi by virtue of demonstrating that their spray dried dispersions are unexpectedly generally better than dispersions produced as disclosed in Nakamichi, by rotary evaporation and by twin screw extrusion. It is accordingly respectfully submitted that patentability with respect to Nakamichi has been conclusively demonstrated.

Further, neither of the Japanese references anticipates or renders Applicants' invention obvious.

Jp 57-176907 does not disclose a composition comprising a dispersion of spray dried HPMCAS plus sparingly soluble drug. Examples 1-4 of Jp 57-176907

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specify spray drying, but not with HPMCAS. Example 5 specifies HPMCAS, but states that the solvent was "evaporated off", not spray dried. Of Examples 6-12, Examples 7-12 each specify a polymer other than HPMCAS and also state that "[t]he solution was made into a powder in same manner as in Example 5". Presumably this means the powder was generated by the same process of simple evaporation described in Example 5 (clearly Example 5 employed simple evaporation since that is the reasonable interpretation of drying with Petri dishes over an evaporative bath). Example 6 specifies HPMCAS, but also states that the solution was made into a powder in the same manner as in Example 5. Presumably then, Example 6 also employed the same simple evaporation method as Example 5. Thus it is not possible for this reference to anticipate since it does not disclose a composition comprising a spray dried dispersion of HPMCAS and a sparingly soluble drug.

The same is true with respect to JP 2-15027. That is, it is respectfully submitted that the rejection of the cited claims as being anticipated by Jp-2-15027 is misplaced since no spray dried HPMCAS embodiment is disclosed. For that matter, the examples of JP 2-15027 do not disclose solvent processing of any type. Rather, the JP 2-15027 description refers to milling while the Examples also disclose a milling process.

It is well accepted that the standard for anticipation is one of strict identity, meaning that for prior art to anticipate, it must contain all of the essential elements. Hybritech Inc. v. Monoclonal Antibodies, Inc.231 USPQ 81 (Fed Cir 1986). See In re Donohue, 226 USPQ 619 (Fed Cir 1985) where it was stated:

> an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device.

As Applicants discuss above, spray drying produces a product having unexpectedly good properties in terms of drug solubility. Spray drying is not simply another way for producing the same dispersion as other processes. Applicants have demonstrated this abundantly, both in their specification and by means of the Declaration of Dwayne T. Friesen previously submitted.

Since neither of the Japanese references discloses a composition comprising a spray dried dispersion comprising HPMCAS and a sparingly soluble drug, the references cannot anticipate. Because the references do not disclose a composition comprising a spray dried dispersion comprising HPMCAS and a sparingly soluble drug, one of ordinary skill in the art would be unaware of the unexpectedly good

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properties exhibited by such compositions as demonstrated by Applicants examples and the Rule 112 Declaration. Only Applicants have demonstrated those properties, and to hold Applicants' invention as obvious is tantamount to using that which only the inventors have taught against them, in hindsight fashion, which is well accepted to be forbidden. W. L. Gore & Associates, Inc. v Garlock, Inc., 220 USPQ 302 (CAFC 1983). Accordingly, it is respectfully submitted that Applicants are patentable over all of the art.

In view if the foregoing amendments and comments, it is submitted that this application is in condition for allowance. A Notice of Allowance is accordingly courteously requested.

Respectfully Submitted,

Date: March 7, 2002

James T. Jones
Attorney for Applicants
Reg. No. 30,561

Pfizer Inc.
Eastern Point Road
Groton, Connecticut 06340
860-441-4903

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VERSION MARKED UP TO SHOW CHANGES MADE

1. (Once Amended) A composition comprising a spray dried solid dispersion, which dispersion comprises a sparingly water-soluble drug and hydroxypropylmethylcellulose acetate succinate (HPMCAS) [HPMCAS], said dispersion providing a maximum concentration of said drug in a use environment that is higher by a factor of at least 1.5 relative to a control composition comprising an equivalent quantity of undispersed drug.

2. (Once Amended) A composition as defined [decribed] in claim 1, wherein said drug has a dose to aqueous solubility ratio greater than 100.

6. (Once Amended) A composition as defined in claim 1, wherein said use environment is model fasted duodenal (MFD) solution [MFD].

7. (Once Amended) A composition of matter comprising a spray-dried solid dispersion, which dispersion comprises a sparingly soluble drug and HPMCAS, said dispersion exhibiting a maximum supersaturated concentration in MFD solution which is higher by a factor of at least 1.5 relative to the equilibrium concentration exhibited by a control composition comprising an equivalent quantity of undispersed drug.

8. (Once Amended) A composition as defined [decribed] in claim 7, wherein said drug has a dose to aqueous solubility ratio greater than 100.

14. (Once Amended) A composition as defined [decribed] in claim 11, wherein said drug has a dose to aqueous solubility ratio greater than 100.

15. (Once Amended) A composition comprising a spray dried solid dispersion, which dispersion comprises a sparingly water-soluble drug and HPMCAS, said dispersion effecting, *in vivo*, an area under a curve (AUC) plotting the serum or plasma concentration of drug along the ordinate against time on the abscissa [AUC] that is higher by a factor of at least 1.25 relative to a control composition comprising an equivalent quantity of undispersed drug.

18. (Once Amended) A composition as defined [decribed] in claim 15, wherein said drug has a dose to aqueous solubility ratio greater than 100.

22. (Once Amended) A composition as defined in claim 1, wherein the concentration of drug in MFD solution falls to no less than 25% of the maximum supersaturated concentration during the 15 minutes following the time at which the maximum supersaturated concentration is reached.

28. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is a glycogen phosphorylase inhibitor.

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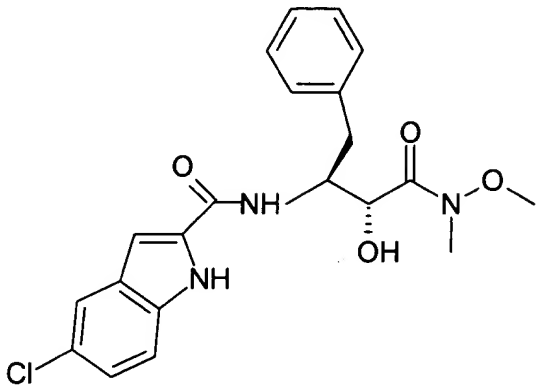
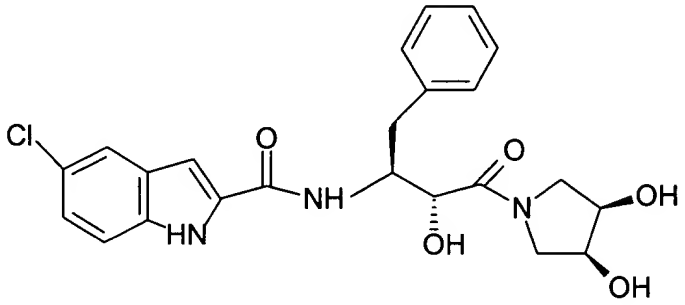
29. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is



or a pharmaceutically acceptable salt thereof.

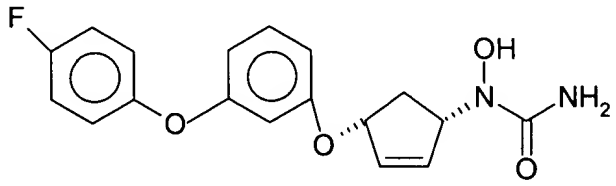
30. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is



or a pharmaceutically acceptable salt thereof.

31. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is a 5-lipoxygenase inhibitor.

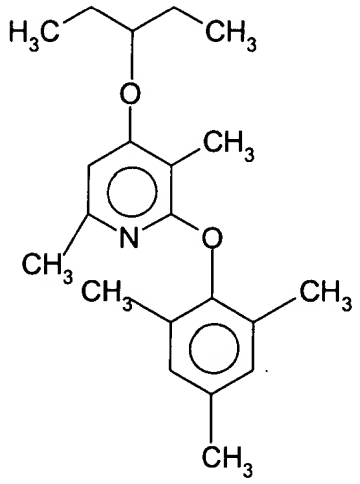
32. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is



or a pharmaceutically acceptable salt thereof.

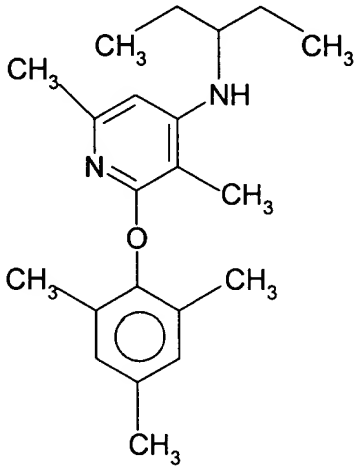
33. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is a corticotropic releasing hormone (CRH) [CRH] inhibitor.

34. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is



or a pharmaceutically acceptable salt thereof.

35. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is



or a pharmaceutically acceptable salt thereof.

36. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is an antipsychotic.

37. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is ziprasidone.

38. (Once Amended) A composition as defined in claims 1, 7, 11, or 15, wherein said drug [compound] is selected from griseofulvin, nifedipine, and phenytoin.

EXHIBIT A

PATENT PC9674AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo, et al. : Examiner: W. Benston Jr.

SERIAL NO.: 09/131,019 : Art Unit: 1615

FILED: August 7, 1998 :

FOR: Solid Pharmaceutical Dispersions
With Enhanced Bioavailability

Assistant Commissioner For Patents
Washington, D.C. 20231

Response Under Rule 116

Sir:

This is in response to the FINAL Office Action of April 11, 2000, the term for response having been extended three (3) months by including the appropriate fee and petition herewith. Reconsideration in light of the comments which follow and the Rule 132 Declaration included herewith is respectfully requested.

The Interview of Sept 26, 2000

The helpful interview held between the undersigned and Examiner Page on September 26, 2000 is acknowledged with gratitude. No separate summary of that interview is believed needed as the Interview Summary Record written by the Examiner is believed to accurately reflect the substance thereof.

The Invention

The invention relates to a composition comprising a spray dried solid dispersion. The dispersion comprises a sparingly water soluble drug and HPMCAS. The dispersion provides a maximum concentration of the drug in a use environment that is higher by a factor of at least 1.5 relative to a control composition comprising an equivalent quantity of undispersed drug. Importantly, the inventors have discovered that spray-dried dispersions of a sparingly soluble drug in HPMCAS unexpectedly perform substantially better than dispersions formed by other methods disclosed in the literature, including Nakamichi et al., US 5,456,923, over which the application stands finally rejected.

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The rejection

As noted above, the application stands rejected over a single reference, US 5,456,923, the Examiner having stated:

> Applicant's arguments filed 12-23-99 have been fully considered but they are not persuasive.
>
> Applicants arguments that the cited reference of Nakamichi et al, does not teach/suggest spray drying is not persuasive as said reference of record clearly teaches a composition comprising a spray dried solid dispersion (col 2, line-8-16; col 2, L 43, col 5, L50-57 0
>
> It would be prima facie obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Nakamichi et al. The motivation lies in the composition comprising a spray dried solid dispersion of active agents. [Page 2 of the Office Action]

Applicants' Traversal

Applicants maintain their position that Nakamichi does not teach/suggest spray drying, and the discussion from Applicants previous response mailed on February 9, 2000 is incorporated herein in this regard. Even allowing, for the sake of argument only, that Nakamichi did suggest spray drying, there is no suggestion in Nakamichi that spray drying produces much better dispersions than other methods also disclosed in the literature, including in Nakamichi. In traversal of Nakamichi, Applicants herein demonstrate that their spray dried dispersions are unexpectedly better/superior to anything that Nakamichi discloses. Based on Applicants' superior, unexpected results relative to Nakamichi, it is respectfully submiited that their invention is patentable thereover.

Applicants arguments are based, *inter alia*, on data provided in their application. Applicants have further provided a Rule 132 Declaration demonstrating the patentability of their invention relative to Nakamichi. The data and the Declaration are discussed below.

Argument

Nakamichi discloses and claims solid dispersions made by passing a mixture of polymer and drug through a "twin screw compounding extruder". Nakamichi describes three operating examples directed to making his dispersions with HPMCAS (Examples 1, 6, and 7). In other examples (Test Examples 3, 10, and 13) Nakamichi demonstrates that his dispersions perform roughly equivalently to those made "by the solvent process" (made as exemplified in Comparative Examples 1, 2, and 3). The parameter he uses to demonstrate equivalence between dispersions made by twin screw extrusion and solvent processing is solubility. The comparative

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"solvent process" chosen by Nakamichi, as disclosed in his Comparative Examples 1, 2, and 3, involves slow evaporation of solvent from a solution of drug and HPMCAS using a rotary evaporator, followed by pulverizing the resulting material in a "table-top compact mill." The particle size used in the comparative test is in the 65- to 100-mesh range.

Nakamichi provides a first demonstration to show equivalence between HPMCAS dispersions made by twin screw extrusion and those made by solvent processing in his Example 1 (Column 6, lines 30 to 55), his comparative Example 1 (column 8, lines 30 to 40), and his Test Example 3 (column 9, lines 48 to 67).. Nakamichi compares his twin screw extruded composition comprising one part "Compound A" and five parts HPMCAS-MF (Example 1) with a comparative composition made by a "solvent process" (Comparative Example 1), the comparative data being presented in Test Example 3. Table 1 in Test Example 3 shows that the twin screw extruded and comparative "solvent process" compositions were judged to have approximately the same solubility values (155 µg/mL and 146 µg/mL, respectively).

Nakamichi provides a second demonstration, to demonstrate equivalence between HPMCAS dispersions made by twin screw extrusion and those made by solvent processing in his Example 6 (Column 7, lines 40 to 53), his comparative Example 2 (column 8, lines 43 to 53), and his Test Example 10 (column 11, lines 10 to 36). Nakamichi compares his twin screw extruded composition comprising one part (300 grams) of nifedipine and five parts (1500 g) of HPMCAS-MF (Example 6) with a comparative composition made by a "solvent process" (Comparative Example 2). The comparative data are presented in Test Example 10. Table 2 in Test Example 10 shows that the twin screw extruded composition solubility was judged to be "close to that" of the comparative "solvent process" composition (26.3 µg/mL and 28.6 µg/mL, respectively).

In a third demonstration of equivalence a third comparison is made between a twin screw extruded Nakamichi composition comprising one part oxbutynin and five parts HMPCAS-MF (Example 7, Column 7, lines 55 to 67) and a comparative "solvent process" composition (Comparative Example 3, Column 8, lines 55 to 67); The comparative data are presented in Test Example 13. As between the two compositions, one "solubility value" was judged to "approximate" the other (Test Example 13, Column 11, line 59 to Column 12, line 23; 473.4 µg/mL for the twin screw and 490.1 µg/mL for the solvent process).

Thus, using solubility of the drug of interest as a measuring stick, Nakamichi's data tend to support that a dispersion of drug in HPMCAS-MF made by Nakamichi's twin screw extrusion process performs roughly the same as a dispersion of drug in HPMCAS-MF made by a "solvent process". The following Table summarizes Nakamichi's data and correlates it with Example numbers, Comparative Example numbers, and Test Example numbers.

Nakamichi Data For Comparison With Applicants

Drug/Polymer	Example - Result	Comp. Ex. – Result	Data In
Cmpd A/HPMCAS	1 – 155 µg/ml	1 – 146 µg/ml	Test Ex. 3
nifedipine/HPMCAS	6 – 26.3 µg/ml	2 – 28.6 µg/ml	Test Ex. 10
oxybutynin/ HPMCAS	7 – 473.4 µg/ml	3 – 490.1 µg/ml	Test Ex. 13

The above portion of Applicants' traversal summarizes the main point of the Nakamichi reference - - that twin screw extrusion produces dispersions that are roughly equivalent, in terms of drug solubility, to dispersions produced by solvent processing, disclosed in Nakamichi as rotary evaporation. The following portion of Applicants traversal demonstrates that Applicants' dispersions, in terms of solubility, are unexpectedly better than Nakamichi.

In the instant application, Applicants demonstrate unexpectedly superior dissolution performance or maximum supersaturated concentration ("solubility" in Nakamichi's terms) for their spray-dried dispersions relative to those made via a "solvent process" – this is, slow evaporation in a rotary evaporator.

A first of Applicants' comparisons is between a dispersion made by spray drying a methanolic solution containing 10 wt% Compound 3 and 90 wt% HPMCAS-HF (Example 24, page 39 of the instant application), and a corresponding composition made via "solvent process" by slow evaporation using a rotary evaporator (Comparative Example C9, pages 39-41 of Applicants' specification). The spray-dried dispersion of Applicants' Example 24 provided a drug concentration of 128 µg/mL within 3 minutes, whereas the dispersion made by rotary evaporation – equivalent to Nakamichi's "solvent process" – produced a maximum drug concentration of only 3.9 µg/mL even after 40 minutes.

A second of Applicant's comparisons is made between a spray dried composition comprising 10 wt% of Compound 6 (phenytoin) and 90 wt% HPMCAS-

MF (Example 29, pages 50-51), and a comparative composition made via "solvent process" in Comparative Example C13 (same pages). The spray-dried dispersion (Example 29) produced a drug concentration of 97 μg/mL within 3 minutes and a maximum drug concentration of 99 μg/mL – the maximum possible, since the theoretical C_{max} was only 96 μg/mL. The dispersion produced by rotary evaporation (Example C13) dissolved more slowly, reaching a maximum value of 90 μg/mL after 90 minutes. The AUC_{90} value for the spray-dried dispersion was 8520 min^{-1} μg/mL, 1.35-fold that of the rotary-evaporated dispersion (6330 min^{-1} μg/mL). This comparison again demonstrates that Applicants' spray-dried dispersions result in higher drug concentrations that are produced rapidly and that are sustained, relative to dispersions produced by solvent processing.

It is again noted that Nakamichi sought to show that his twin screw extruded dispersions are equivalent to those produced by solvent processing, rotary evaporation being the only kind of solvent processing exemplified in Nakamichi (see all of Nakamichi's Comparative Examples 1-5). By demonstrating that their spray-dried dispersions are superior to dispersions made by the rotary evaporation "solvent process," disclosed in Nakamichi, Applicants have, by extension, also demonstrated that that their spray-dried dispersion are also better than Nakamichi's twin-screw extruded dispersions as well, since Nakamichi teaches that dispersions made by rotary evaporation and twin-screw extrusion perform equivalently.

Applicants' Rule 132 Declaration

To further demonstrate the unexpected good results afforded by their invention relative to Nakamichi, Applicants have further included, as part of this response, a Rule 132 Declaration which demonstrates that spray dried dispersions of a sparingly soluble drug are unexpextedly superior to the rotary evaporated dispersions disclosed in Nakamichi, even when the dispersions are otherwise compositionally the same. To demonstrate unexpected results, Applicants have compared the concentrations of three drugs from their application, made up as spray dried dispersions (SDDs) with the concentrations of the same three drugs made up as rotary evaporated dispersions (REDs). The following three drugs were used in the Trials that are used in the Declaration:

Compound 1, the compound disclosed in Applicants Example 1, page 22;
Compound 5, nifedipine, as disclosed in Applicants' Example 28; page 46;
Compound 8, the compound disclosed in Applicants' Example 31; page 54

In the Declaration, each of the three Compounds was made into a spray dried composition (SDD) with HPMCAS. Each of the Compounds was also made into a rotary evaporated dispersion (RED) with HPMCAS.

Applicants ran three dissolution Trials, with each Trial involving a separate dissolution medium and/or different conditions, as noted below. The object of the three Trials was to compare the solubility/concentration of each of the above three Compounds as an SDD versus as an RED. Plain crystalline drug added to solution (i.e., no dispersing polymer, spray drying, or rotary evaporation) was used as a control, as appropriate. Each trial is reflective of different conditions, as follows:

Trial 1 - - Used the same dissolution test method as described in Applicants' specification in Example 3, except that the phosphate buffered saline was substituted for model fasted duodenal solution as the dissolution media. The dissolution medium was maintained at 37°C during dissolution testing. Sample work up was by centrifugation at 13,000 G for one minute;

Trial 2 - - Used the test method described in Nakamichi. Nakamichi's method used JP-2 test solution at 25°C as a dissolution medium and 40,000 G as a centrifugation speed for one hour.

Trial 3 - - Used a modified version of the Nakamichi method. The method used Nakamichi's JP-2 test solution, but under the more physiologically relevant conditions of 37°C (i.e., human body temperature), gentler centrifugation conditions - - a centrifugation speed of 13,000 G for 1 minute, and data collection during the first three hours of dissolution testing.

Each Trial involved three Runs, with each Run involving one of the three Compounds identified above. Each Run involved comparing the concentration of a single Compound from an SDD with the concentration of that Compound from the corresponding Compound RED. In each run a control of crystalline compound (no HPMCAS, no spray drying or rotary evaporation) was used. Each dissolution medium was sampled at a number of time points up to three hours, the concentration of time was determined, and these data were used to calculate the area under the curve (AUC) during the three hours. The three hour time period for sampling is submitted to be physiologically relevant, as opposed to Nakamichi's single time point of 1440 minutes (24 hours).

Cmax, the highest concentration of Compound achieved during the three hours, was also determined.

The Trials are discussed as follows, with Table numbers referring to those in the Trial Protocol which forms part of the Declaration.

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The data for Trial 1 is shown in Table 2 (raw data) and Table 3 (Summary) in the Trial Protocol. The data demonstrates that the Compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 12,900 and 28,400, respectively) as compared to the compound 1 and 5 rotary evaporated dispersions (AUC values of 3500 and 19,600). Applicants' SDD values for Compounds 1 and 5 were thus 268% and 44% higher, respectively, than the corresponding RED values. The data shows that the compound 8 SDD and RED were roughly equivalent (AUC values of 57,000 versus 58,100). The Cmax value for all three of the SDDs (93, 196, and 440, respectively) were unexpectedly higher than the corresponding Cmax values for the REDs (24, 129, and 380, respectively).

The data for Trial 2 is shown in Table 4 (raw data) and Table 5 (summary) in the Trial protocol. The data demonstrates that the compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 3400 and 25,200, respectively) than the compound 1 and 5 rotary evaporated dispersions (AUC values of 1400 and 10,500). Applicants' SDD values for Compounds 1 and 5 were thus 142% and 140% higher, respectively, than the corresponding RED values. The Cmax values for the compound 1 and 5 SDDs (23 and 191, respectively) were also unexpedtedly higher than for their RED counterparts (13 and 113). The data for compound 8 (Run 6), including the Cmax, was corrupted for both the SDD and the RED. Although the exact reason is not certain, it is believed that the severe conditions of the Nakamichi centrifugation (40,000 G for an hour) may have spun the polymer and polymer-associated compund (both the SDD and RED) out of solution, effectively preventing any measurements of concentration or Cmax.

The data for Trial 3 is shown in Table 6 (raw data) and Table 7 (summary) in the Trial Protocol. This Trial was conducted as a modification of the Nakamichi method and used Nakamichi's dissolution test solvent, but also used gentler (centrifuge) sample workup than Nakamichi (13,000 G for 1 minute as opposed to 40,000 G for 1 hour). Data for Trial 3 was obtained in the case of all three test drugs, as opposed to Trial 2. The data demonstrates that all three of the Compound 1, 5, and 8 dispersions showed unexpectedly higher solubility for the physiologically relevant time period, 0 to 180 minutes (AUC values of 5100, 35,600, and 49,300, respectively) than the three Compound 1, 5, and 8 REDs (1600, 17,000, and 36,200). Applicants' SDD values for Compounds 1, 5, and 8 were thus 218%, 109% and 36% higher, respectively, than the corresponding RED values. The Cmax value

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for each of the SDDs (30, 220, and 300, respectively) was unexpectedly higher than the Cmax values for the REDs (14, 113, and 220).

In summary, Applicants' data demonstrates for the physiologically relevant test interval of 0 to 180 minutes that:

A. Applicants' SDDs generated much higher concentrations of drug in seven out of eight runs occurring over the three trials. The eighth run showed roughly equivalent values of AUC. The ninth run was corrupted and yielded no useful data.

B. Applicants' SDD Cmax was higher than the corresponding RED Cmax for every run where Cmax could be measured (8 out of 8 runs).

C. For the one compound in common between Applicants and Nakamichi, i.e., nifedipine (Compound 5), that Applicants' were unexpectedly much better in terms of both AUC and Cmax.

The data accordingly demonstrate that Applicants' SDDs are generally unexpectedly much better than the REDs disclosed in Nakamici. In view of the foregoing comments and the Rule 132 Declaration, it is respectfully submitted that Applicants' claims define patentable subject matter, and that this application is accordingly in condition for allowance. A Notice Of Allowance is accordingly respectfully requested.

Respectfully Submitted,

Date: Oct. 9, 2000

James T. Jones
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EXHIBIT B

PATENT PC9674AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: **William J. Curatolo, et al.**

SERIAL NO.: **09/131,019** : Examiner: **W. Benston Jr.**
: Art Unit: **1615**

FILED: **August 7, 1998** :

FOR: **Solid Pharmaceutical Dispersions With Enhanced Bioavailability**

Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Dwayne T. Friesen, declare that:

1. I was awarded the degree of Bachelor of Science in Chemistry in 1975 by California State College at Bakersfield, and subsequently was awarded a Ph.D. in Physical Chemistry in 1980 at Oregon State University. I have been employed by Bend Research, Inc., of which I am also part owner, up to the present time. My former title was Director of Research. My current title is Vice President, Research. I am a member of the Board of Directors of Bend Research, Inc.

2. Bend Research, Inc., is part-owned by Pfizer, Inc., the Assignee of the above-identified US application.

3. By virtue of my expertise and work on the project area of pharmaceutical dispersion technology, from which this application originated, I am aware of the application which, as stated above, is owned by Pfizer, Inc., by virtue of an assignment recorded at Reel/Frame 9148/0782. I have read the Final Office Action which was mailed on April 11, 2000 and am aware of the rejection of claims 1 – 38, over US patent 5,456,923 (hereinafter "Nakamichi") as set forth therein.

4. Under my direction, and as described in the Experimental Protocol attached hereto, three Trials were conducted whereby, in each Trial, a spray dried dispersion

(SDD) and a rotary evaporated dispersion (RED) were made for each of three drugs, dissolution tested, and compared. The drugs were, respectively:

Compound 1, the compound disclosed in Applicants' Example 1;
Compound 5, nifedipine, as disclosed in Applicants' Example 28;
Compound 8, the compound disclosed in Applicants' Example 31;

5. The three Trials, including the results therefrom, are reported in detail in the attached Experimental Protocol, which forms a part of this Declaration and is incorporated by reference herein.

6. The object of the three Trials was to compare the dissolution of each of the above three compounds in spray dried dispersions (SDDs) versus rotary evaporated dispersions (REDs); plain crystalline drug added to solution (i.e., no dispersing polymer, spray drying, or rotary evaporation) was used as a control, as appropriate. Each trial is reflective of different conditions, as follows:

Trial 1 - - Used the same dissolution test method as described in Applicants' specification in Example 3, except that the phosphate buffered saline was substituted for model fasted duodenal solution as the dissolution media. The dissolution medium was maintained at 37°C during dissolution testing. Sample work up was by centrifugation at 13,000 G for one minute;

Trial 2 - - Used the test method described in Nakamichi. Nakamichi's method used JP-2 test solution at 25°C as a dissolution medium and 40,000 G as a centrifugation speed for one hour;

Trial 3 - - Used a modified version of the Nakamichi method. The method used Nakamichi's JP-2 test solution, but under the more physiologically relevant conditions of 37°C (i.e., human body temperature), gentler centrifugation conditions -- a centrifugation speed of 13,000 G for 1 minute, and data collection during the first three hours of dissolution testing.

7. In each trial, samples of each drug were taken from the individual dissolution media at various time points. For Trials 1 and 3, sample time points were 0, 5, 30, 60, 120, 180 minutes, and 1440 minutes; for Trial 2, sample time points were 0, 60, 120, 180 minutes, and 1440 minutes. 1440 minutes (24 hrs) was included because that is the single time point at which Nakamichi made his dissolution concentration

measurements. The Nakamichi time point is, however, considered physiologically irrelevant since absorption of a drug takes place primarily during the first several (i.e., 1-4) hours following ingestion. Data for the time interval AUC of 0 to 180 minutes, AUC_{180}, is reported in the Experimental Protocol as being physiologically relevant. From the data, Applicants calculated the area under the curve (AUC) for the 0 to 180 minute time interval (AUC_{180}) from the measured drug concentrations, and measured the maximum concentration of dissolved drug during that time period, $Cmax_{180}$.

8. The data for Trial 1 is shown in Table 2 (raw data) and Table 3 (Summary) in the Trial Protocol. The data demonstrates that the Compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 12,900 and 28,400, respectively) as compared to the Compound 1 and 5 rotary evaporated dispersions (RED) (AUC values of 3500 and 19,600). Applicants' SDD values for Compounds 1 and 5 were thus 268% and 44% higher, respectively, than the corresponding RED values. The data shows that the Compound 8 SDD and RED were roughly equivalent (AUC values of 57,000 versus 58,100, respectively). The $Cmax_{180}$ value for all three of the SDDs (93, 196, and 440, respectively) were unexpectedly higher than the corresponding $Cmax_{180}$ values for the REDs (24, 129, and 380, respectively).

9. The data for Trial 2 is shown in Table 4 (raw data) and Table 5 (summary) in the Trial Protocol. The data demonstrates that the Compound 1 and 5 spray dried dispersions (SDDs) showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values at 180 minutes of 3400, and 25,200, respectively) than the Compound 1 and 5 rotary evaporated dispersions (RED) (AUC values of 1400 and 10,500). Applicants' SDD values for Compounds 1 and 5 were thus 142% and 140% higher, respectively, than the corresponding RED values. The $Cmax_{180}$ values for the Compound 1 and 5 SDDs (23 and 191, respectively) were also unexpectedly higher than for their RED counterparts (13 and 113, respectively). The data for Compound 8, including the $Cmax_{180}$, was corrupted for both the SDD and the RED. Although the exact reason is not certain, the undersigned believes that the severe conditions of the Nakamichi centrifugation (40,000 G for one hour) may have spun the polymer and polymer-

associated compound (both the SDD and RED) out of solution, effectively preventing any measurements of concentration or Cmax.

10. The data for Trial 3 is shown in Table 6 (raw data) and Table 7 (summary) in the Trial Protocol. This Trial was conducted as a modification of the Nakamichi method and used Nakamichi's dissolution test solvent, but used gentler (centrifuge) sample workup than Nakamichi (13,000 G for 1 minute as opposed to 40,000 G for 1 hour. Data for Trial 3 was obtained in the case of all three test drugs, as opposed to Trial 2. The data demonstrates that all three of the Compounds 1, 5, and 8 SDDs showed unexpectedly higher drug concentrations for the physiologically relevant time period, 0 to 180 minutes (AUC values of 5100, 35,600, and 49,300, respectively) than the three Compound 1, 5, and 8 REDs (1600, 17,000, and 36,200, respectively). Applicants' SDD values for Compounds 1, 5, and 8 were thus 218%, 109% and 36% higher, respectively, than the corresponding RED values. The $Cmax_{180}$ value for each of the SDDs (30, 220, and 300, respectively) were unexpectedly higher than the $Cmax_{180}$ values for the REDs (14, 113, and 220, respectively).

11. In summary, Applicants' data demonstrates for the physiologically relevant test interval of 0 to 180 minutes that:

A. Applicants' SDDs generated much higher concentrations of drug in seven out of eight runs occurring over the three trials. The eighth run showed roughly equivalent values of AUC. The ninth run was corrupted and yielded no useful data.

B. Applicants' SDD $Cmax_{180}$ was higher than the corresponding RED Cmax for every run where $Cmax_{180}$ could be measured (8 out of 8 runs).

C. For the one compound in common between Applicants and Nakamichi, i.e., nifedipine (Compound 5), Applicants' SDDs were unexpectedly much better in terms of both AUC and $Cmax_{180}$.

12. The data accordingly demonstrate that Applicants' SDDs are generally unexpectedly much better than the REDs disclosed in Nakamichi.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

10-6-00
Date

Dwayne T. Friesen

Experimental Protocol

Examples 1-3; Preparation of Spray Dried Dispersions

Amorphous solid dispersions of Compound 1, Compound 5 [nifedipine], or Compound 8, with HPMCAS, were made by mixing the compound in solvent together with HPMCAS to form a solution. For Example 1, the solution comprised 0.33 wt% Compound 1, 2.27 wt% HPMCAS-MF, and 97.40 wt% methanol/acetone (86 wt%/14 wt%). For Example 2, the solution comprised 0.51 wt% Compound 5, 2.55 wt% HPMCAS-MF, and 96.94 wt% ethanol/methylene chloride (70 vol% / 30 vol%). For Example 3, the solution comprised 0.42 wt% Compound 8, 0.83 wt% HPMCAS-LG, and 98.75 wt% methanol/acetone (50 wt%/50 wt%). A portion of each solution was pumped into a "mini" spray-dryer apparatus of the type shown in FIGURE 1 of the pending patent via a syringe pump. For Example 1, the solution was pumped at a rate of 70 mL/hr. For Examples 2 and 3, the solution was pumped at a rate of 60 mL/hr. The spray solution was metered using a Cole Parmer 74900 Series rate-controlling syringe pump. The solution was pumped into a Spraying Systems Co. two-fluid nozzle, Model Number SU1A, with nitrogen as the atomizing gas. The nitrogen was pressurized and heated to a temperature of 110°C to 120°C. The solution was sprayed from the top of an 11-centimeter-diameter stainless-steel chamber. The resulting solid amorphous dispersions were collected on Whatman® 1 filter paper, dried under vacuum, and stored in a desiccator.

Table 1 summarizes the solution preparation variables of the spray dried dispersions (SDD).

Table 1. Preparation Of Spray Dried Dispersions (SDDs)

Ex. No.	Cmpd Mass (g)	Cmpd No.	Polymer Mass (g)	Polymer	Solvent Mass (g)	Solvent
Ex1	3.50	1	24.51	HPMCAS-MF	1050	86 wt% methanol/ 14 wt% acetone
Ex2	2.51	5	12.50	HPMCAS-MF	475	70 vol% ethanol/ 30 vol% methylene chloride
Ex3	0.51	8	1.01	HPMCAS-LG	120	50 wt% methanol/ 50 wt% acetone

Comparative Examples 1-3: Preparation of Rotary Evaporated Dispersions

A portion of each of the solutions of Compounds 1, 5, and 8, described in Table 1 above (Examples 1-3) were added to round-bottom flasks, and the solvents were removed using a rotary evaporator (as described by Nakamichi.) The flasks were rotated at 150 rpm, and the water bath was maintained at 50°C. The resulting solid material was stored under vacuum overnight at room temperature and then removed from the flask, pulverized, and size-selected via sieving to provide a 60 to 100 mesh powder.

Trial 1: Runs 1-3

The SDDs of Examples 1-3, and the rotary-evaporated material from Comparative Examples 1-3, were evaluated in an *in vitro* dissolution trial using the "centrifuge" method. This is the same test described in Example 3 of the pending Patent except that the dissolution solution was phosphate buffered saline (PBS) solution, as this solution is more similar to the JP2 solution used by Nakamichi. Samples were withdrawn and analyzed at different times. In this test, 2.88 mg of the SDD of Example 1 or the rotary evaporated dispersion (RED) of Comparative Example 1, 2.15 mg of the SDD of Example 2 or the RED of Comparative Example 2, or 2.70 mg of the SDD of Example 3 or the RED of Comparative Example 3, was added to a microcentrifuge tube. Each trial run was performed in duplicate. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL of phosphate buffered saline (PBS) at pH 6.5 and 290 mOsm/kg was added. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 5, 30, 60, 120, 180, and 1440 minutes. Crystalline Compound 1, Compound 5, and Compound 8 (0.36 mg, 0.36 mg, and 0.90 mg, respectively) were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 2.

Table 2. Results of Trial 1

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 1/Cmpd 1 SDD	0	0	
	5	37	
	30	58	
	60	70	
	120	80	
	180	93	12,900
	1440	120	
Trial 1 Run 1/Cmpd 1 RED	0	0	
	5	7	
	30	15	
	60	19	
	120	23	
	180	24	3500
	1440	28	
Trial 1 Run 1/Cmpd 1 Crystalline Cmpd (Control)	0	0	
	5	<2	
	30	<2	
	60	<2	
	120	<2	
	180	<2	<400
	1440	<2	
Trial 1 Run 2/Cmpd 5 SDD	0	0	
	5	196	
	30	189	
	60	192	
	120	139	
	180	110	28,400
	1440	48	

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 2/Cmpd 5 RED	0	0	
	5	47	
	30	85	
	60	113	
	120	127	
	180	129	19,600
	1440	55	
Trial 1 Run 2/Cmpd 5 Crystalline Cmpd (Control)	0	0	
	5	5	
	30	5	
	60	7	
	120	7	
	180	6	1100
	1440	8	
Trial 1 Run 3/Cmpd 8 SDD	0	0	
	5	440	
	30	370	
	60	330	
	120	290	
	180	250	57,000
	1440	42	
Trial 1 Run 3/Cmpd 8 RED	0	0	
	5	350	
	30	380	
	60	340	
	120	320	
	180	260	58,100
	1440	14	

Run/Cmpd	Time (min)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 1 Run 3/Cmpd 8 Crystalline Cmpd (Control)	0	0	
	5	<5	
	30	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 3, which shows the maximum concentration of SDD compounds in solution during the first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). Microcentrifuge dissolution test results for SDDs described in Examples 1-3, as well as REDs described in Comparative Examples 1-3, are all shown in Table 3 for comparison.

Table 3. Summary of Table 2

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	93	12,900	120
C1	1	12.5	200	24	3500	28
Crystalline cmpd	1	--	200	<2	<400	<2
Ex 2	5	16.7	200	196	28,400	48
C2	5	16.7	200	129	19,600	55
Crystalline cmpd	5	--	200	7	1100	8
Ex 3	8	33.3	500	440	57,000	42
C3	8	33.3	500	380	58,100	14
Crystalline cmpd	8	--	500	<5	<500	<5

These results show that dispersions formed by spray-drying resulted in increased Compound concentrations.over that of dispersions formed using rotary evaporation.

Trial 2: Runs 4-6

The SDDs of Examples 1-3, and the REDs from Comparative Examples 1-3, were evaluated in the saturation dissolution test described in US Patent 5,456,923 (Nakamichi). In this test, the SDDs and REDs were dosed into JP test solution 2 (0.2 M KH_2PO_4, adjusted to pH 6.8 using NaOH) at 25°C in a shaker bath for 24 hr at 24 cycles/min. Unlike Nakamichi (who sampled only after 24 hours), Applicants sampled the solutions at times that were physiologically relevant since absorption of Compound occurs primarily during the first several (i.e., 1 to 4) hours following ingestion. Samples were taken at 0, 60, 120, 180, and 1440 minutes. The samples were centrifuged at 40,000 rpm for 1 hr. This level of centrifugation may remove polymer and polymer/Compound aggregates from solution leading to an erroneously low estimate of bioavailability. The supernatant was analyzed by HPLC. Crystalline Compound 1, Compound 5, and Compound 8 were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 4.

Table 4. Results of Trial 2

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 4/Cmpd 1 SDD	0	0	
	60	23	
	120	23	
	180	23	3400
	1440	22	
Trial 2 Run 4/Cmpd 1 RED	0	0	
	60	6	
	120	10	
	180	13	1400
	1440	20	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 6/Cmpd 8 Crystalline Cmpd (Control)	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 5, which shows the maximum concentration of Compound in solution during the first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). Saturation dissolution test results for dispersions described in Examples 1-3 , as well as Comparative Examples 1-3, are shown in Table 5 for comparison.

Table 5. Summary of Table 4

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	23	3400	22
C1	1	12.5	200	13	1400	20
Crystalline cmpd	1	--	200	<2	<400	<2
Ex 2	5	16.7	200	191	25,200	28
C2	5	16.7	200	113	10,500	5
Crystalline cmpd	5	--	200	5	800	5
Ex 3	8	33.3	500	<5	<500	<5
C3	8	33.3	500	<5	<500	<5
Crystalline cmpd	8	--	500	<5	<500	<5

These results also show that dispersions formed by spray-drying resulted in equal or greater Compound concentration relative to that of materials formed using rotary evaporation. In some cases, particularly for Compound 8, Nakamichi's test method shows extremely low Compound levels at all times. However, other more physiologically relevant tests show much

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 2 Run 4/Cmpd 1 Crystalline Cmpd (Control)	0	0	
	60	<2	
	120	<2	
	180	<2	<400
	1440	<2	
Trial 2 Run 5/Cmpd 5 SDD	0	0	0
	60	191	
	120	160	
	180	138	25,200
	1440	28	
Trial 2 Run 5/Cmpd 5 RED	0	0	
	60	35	
	120	83	
	180	113	10,500
	1440	5	
Trial 2 Run 5/Cmpd 5 Crystalline Cmpd (Control)	0	0	
	60	5	
	120	5	
	180	5	800
	1440	5	
Trial 3 Run 6/Cmpd 8 SDD	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	
Trial 2 Run 6/Cmpd 8 RED	0	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

higher Compound levels. Comparing results from Table 5 above to results in Table 2 of US Patent 5,456,923 shows that the rotary-evaporated material of Comparative Example 2 improves Compound 5 (nifedipine) concentration over that of crystalline Compound alone (as shown in US Patent 5,456,923); however, the spray-dried dispersion of Example 2 sharply improves Compound 5 concentration over that of the corresponding RED.

Trial 3: Runs 7-9

To demonstrate that the test differences between Nakamichi's and our test methods that are likely most relevant are the sample times and level of centrifugation, Applicants conducted the following dissolution test that used the method of Nakamichi (US Patent 5,456,923) except using: (1) shorter samples times and (2) less severe centrifugation. The SDDs of Examples 1-3, and the REDs from Comparative Examples 1-3, were evaluated in a saturation dissolution test similar to that described in US Patent 5,456,923. The saturation dissolution test was performed with the modification of less stringent centrifugation to allow polymer and the Compound in the form of polymer/Compound aggregates to remain in solution. In this test, the spray dried dispersions (SDDs) and rotary evaporated dispersions (REDs) were dosed into JP Test Solution 2 (0.2 M KH_2PO_4, adjusted to pH 6.8 using NaOH) at 25°C in a shaker bath for 24 hr at 24 cycles/min. Samples were taken at 0, 5, 30, 60, 120, 180, and 1440 minutes. The samples were centrifuged at 13,000 rpm for 1 minute. The supernatant was analyzed by HPLC. Crystalline Compound 1, Compound 5, and Compound 8 were also tested for comparison. The concentrations of Compound obtained in these samples are shown in Table 6.

Table 6. Results of Trial 2

SDD = Spray Dried Dispersion

RED = Rotary Evaporated Dispersion

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 3/Run 7 Cmpd 1 SDD	0	0	
	5	26	
	30	28	
	60	29	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
	120	29	
	180	30	5100
	1440	32	
Trial 3/Run 7 Cmpd 1 RED	0	0	
	5	3	
	30	4	
	60	8	
	120	11	
	180	14	1600
	1440	23	
Trial 3/Run 7 Cmpd 1 Crystalline Cmpd (Control)	0	0	
	5	<2	
	30	<2	
	60	<2	
	120	--	
	180	<2	<400
	1440	<2	
Trial 3/Run 8 Cmpd 5 SDD	0	0	
	5	140	
	30	199	
	60	220	
	120	220	
	180	176	35,600
	1440	41	
Trial 3/Run 8 Cmpd 5 RED	0	0	
	5	24	
	30	77	
	60	103	
	120	109	
	180	113	17,000
	1440	39	

Example	Time (hr)	Cmpd Concentration (μgA/mL)	AUC (min*μg/mL)
Trial 3/Run 8 Cmpd 5 Crystalline Cmpd (Control)	0	0	
	5	2	
	30	2	
	60	2	
	120	3	
	180	4	500
	1440	5	
Trial 3/Run 9 Cmpd 8 SDD	0	0	
	5	270	
	30	300	
	60	280	
	120	290	
	180	240	49,300
	1440	133	
Trial 3/Run 9 Cmpd 8 RED	0	0	
	5	104	
	30	174	
	60	220	
	120	220	
	180	210	36,200
	1440	23	
Trial 3/Run 9 Cmpd 8 crystalline Cmpd (Control)	0	<5	
	5	<5	
	30	<5	
	60	<5	
	120	<5	
	180	<5	<500
	1440	<5	

The results of this test are summarized in Table 7, which shows the maximum concentration of Compound in solution during the

first 180 minutes of the test ($Cmax_{180}$), the area under the aqueous concentration versus time curve after 180 minutes (AUC_{180}), and the concentration at 1440 minutes (C_{1440}). The modified saturation dissolution test results for dispersions described in Examples 1-3, as well as Comparative Examples 1-3, are all shown in Table 7 for comparison.

Table 7. Summary Of Table 6

Example	Cmpd No.	Cmpd Conc. in the Dispersion (wt%)	Dosage (μgA/mL)	$Cmax_{180}$ (μgA/mL)	AUC_{180} (min*μg/mL)	C_{1440} (μgA/mL)
Ex 1	1	12.5	200	30	5100	32
C1	1	12.5	200	14	1600	23
Crystalline cmpd	1	--	200	<2	<500	<2
Ex 2	5	16.7	200	220	35,600	41
C2	5	16.7	200	113	17,000	39
Crystalline cmpd	5	--	200	<14	500	5
Ex 3	8	33.3	500	300	49,300	133
C3	8	33.3	500	220	36,200	23
Crystalline cmpd	8	--	500	<5	<500	<5

The Compound concentrations observed for the saturation dissolution tests of Example 6 were greater than the concentrations observed in the tests of Example 5. This is due to less stringent centrifugation of samples for Example 6, which allowed the Compound to remain in solution. These results more clearly show that dispersions formed by spray-drying resulted in increased Compound concentration over that of dispersions formed using rotary evaporation.